IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Linda C. Burkly	Art Unit	: 1642
Serial No.	: 09/234,290	Examiner	: Susan Ungar
Filed	: January 20, 1999		
Title	: TREATMENT FOR INSULIN DEPENDENT DIABETES		

BOX AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

In response to the final action mailed on November 16, 2001, Applicants filed a notice of appeal on May 16, 2002.

(1) Real Party in Interest

The Real Party in Interest is Biogen, Inc., 14 Cambridge Center, Cambridge, MA 02142.

(2) Related Appeals and Interferences

There are no pending related appeals or interferences.

(3) Status of Claims

Claims 25, 28, and 31-36 are pending and under appeal.

(4) Status of Amendments

No amendments are being submitted herewith.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202.

October 15, 2002
Date of Deposit

Maria Keen
Signature

Maria Keen
Typed or Printed Name of Person Signing Certificate

(5) Summary of Invention

The invention relates to a method for the treatment of insulin dependent (type I) diabetes comprising administering to a prediabetic mammal, or a mammal having partial β cell destruction, a composition comprising a soluble fibronectin polypeptide, e.g., a fibronectin polypeptide comprising an EILDV motif, a chimeric fibronectin-toxin molecule, or a fibronectin polypeptide comprising an alternatively spliced non-type III connecting segment of fibronectin.

(6) Issues

(a) Does the specification enable one skilled in the art to practice the invention commensurate in scope with claims 25, 28, and 31-36 as required under 35 U.S.C. § 112, first paragraph?

(b) Are claims 25, 28, and 31-36 indefinite under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention?

(7) Grouping of Claims

The claims should stand or fall together.

(8) Argument

(A) Claims 25, 28, And 31-36 Are Enabled By The Specification.

Claims 25, 28, and 31-36 stand finally rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The pending claims currently under appeal (see Appendix (9)) are directed to a method for treating diabetes in a prediabetic mammal, or a mammal having partial β cell destruction, by administering a soluble fibronectin polypeptide, e.g., a fibronectin polypeptide comprising an EILDV motif, a chimeric fibronectin-toxin molecule, or a fibronectin polypeptide comprising an alternatively spliced non-type III connecting segment of fibronectin.

For a patent to be enabling, it must teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. For the reasons discussed in detail below, Appellant respectfully submits that the present application meets this standard.

It is predictable from the guidance provided in the specification that the claimed methods will work as claimed.

At the time the present application was filed, fibronectin polypeptides were known inhibitors of the VLA-4 activity. Once the Appellant established the correlation between inhibition of the VLA-4-VCAM interaction and the treatment of diabetes, as discussed in detail below, similar results were expected using fibronectin polypeptides.

Appellant discovered that blocking the interaction between the Very Late Antigen-4 receptor (VLA-4) and one of its ligands, Vascular Cell Adhesion Molecule (VCAM-1), delayed the onset of diabetes in a rodent model. The present application provides working examples showing a reduction of diabetes in rodents using VCAM fusion constructs and antibodies to VLA-4. In particular, the application includes an example in which the administration of anti-VLA-4 antibody (R1-2) significantly inhibited onset of diabetes in a non-obese diabetic (NOD) mouse model and the residual beneficial results of the treatment were extended as long a two months after cessation of administration of the antibody. (See, e.g., pages 16-18 and 23 of the specification). Successful results were also observed when a VCAM-Ig fusion protein (VCAM 2D-IgG) was used to block the VLA-4-VCAM interaction. (See Example 5, page 23).

At the time the present application was filed, fibronectin and VCAM were known to be capable of binding to VLA-4 (see e.g., Wayner et al. (1989) *J. Cell. Biol.* 109:1321-1330). Moreover, fibronectin polypeptides and fragments thereof (e.g., the CS-1 domain of fibronectin) were known inhibitors of VLA-4 activity *in vitro* and in numerous *in vivo* models, including autoimmune, transplant rejection and cancer models. The particular sites of fibronectin involved in the interaction with VLA-4 were known to be located in the alternate spliced type IIICS or V region (Guan, J-L et al. (1990) *Cell* 60:53). Two

distinct sites were recognized: the CS1 motif, in which the minimally active sequence is comprised of the LDV sequence and the CS5 motif, in which the minimally active site is localized to the REDV sequence (Massia, S. et al. (1992) *J. Biol. Chem.* 267:14019). The interaction of VLA-4 and the fibronectin CS1 peptide was demonstrated to be functionally important in the process of transendothelial migration of a leukocyte subpopulation *in vitro* (Kuijpers, T. et al. (1993) *J. Exp. Med.* 178:279).

Thus, once the Appellant established the correlation between inhibition of the VLA-4-VCAM interaction and the treatment of diabetes, similar results were expected using fibronectin polypeptides.

Further, strategies involving the use of antibody and/or CS-1 peptide inhibitors of the VLA-4 interactions with VCAM or fibronectin to inhibit immune cell migration to inflammatory sites were known at the time the present application was filed, and have been used since then in numerous *in vivo* models. For example, adhesion of T lymphoblastoid cells to the synovial endothelium of rheumatoid arthritis patients has been abrogated using either an anti-α4 integrin antibody or by the CS1 peptide (Elices, M. et al. (1994) *J. Clin. Invest.* 93:405). CS1 peptide has also been shown to decrease lymphocyte migration through high endothelial venule cells (Ager, A. et al. (1991) *Int. Immunol.* 2:921). IDS Synthetic CS1 tetrapeptides, which block VLA-4 binding to fibronectin, have been shown to reduce accelerated coronary arteriopathy in cardiac allograft animal models (Molossi, S. et al. (1995) *J. Clin. Invest.* 95(6): 2601-2610). Similarly, Korom et al. (1998) *Transplantation* 65:854-859 showed that a 25-mer alternatively spliced CS1 variant of fibronectin effectively inhibited the development of chronic rejection in cardiac allograft recipients, and depressed the expression of key T cell- and macrophage-associated cytokines/chemoattractants. See also, Coito, A.J. et al. (1998) *Transplantation Proc.* 30:939-940 (describing the use of a similar 25-mer fibronectin peptide to abrogate acute rejection and significantly prolong cardiac allograft survival). Inhibition of VLA-4-mediated cell adhesion using fibronectin peptides has also been successfully used to inhibit tumor metastasis and invasion. For example, Saiki, I. et al. (1993) *Jpn. J. Cancer Res.* 84: 326-335 showed prolonged survival of mice

having liver and lung metastasis of lymphoma or melanoma cells, respectively, using a combination therapy of a fusion polypeptide containing the cell binding- and the heparin binding- domain of fibronectin, in combination with anticancer drugs, such as doxorubicin and mitomycin C.

Furthermore, in concluding that the treatment of diabetes is unpredictable, the Examiner relies, in part, on the statement made in the Background section of the present application (page 4, lines 17-18), which provides that in the past there has been little success in treating human diabetes. Appellant submits that the statement about the limited success in treating diabetes in the Background section clearly refers to immunosuppressive and/or immunomodulatory agents for treating diabetes available prior to the present application. In particular, pages 3-4 of the background describe the shortcomings of prior art methods and compositions in treating diabetes. Unlike the generally non-specific modalities to treat diabetes described in pages 3-4 of the background, the present invention demonstrated how specific inhibitors of VLA-4-VCAM interactions effectively prevented immune cell destruction of pancreatic islet β cells, and thus could be used therapeutically to treat diabetes. The statement relied upon by the Examiner, therefore, does not apply to the present invention.

With regard to claim 36, in Paper 14, section 12, pages 12-13, the Examiner states the following.

> One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not teach how to make the alternatively spliced non-type III connecting segment so that it will function as claimed. It is well known in the art that alternative splicing produces products with different amino acid constituents whereby additions to, truncations or deletion of amino acids of the protein product are produced. However, applicant has not enabled all of these types of modified connecting segments because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Appellant respectfully traverses this aspect of the rejection. As described above, at the time the present application was filed, the particular sites of fibronectin involved in

the interaction with VLA-4 were known to be located in the alternate spliced type IIICS or V region (Guan, J-L et al. (1990) *Cell* 60:53). Two distinct sites were recognized: the CS1 motif, in which the minimally active site is comprised of the LDV sequence and the CS5 motif, in which the minimally active site is localized to the REDV sequence (Massia, S. et al. (1992) *J. Biol. Chem.* 267:14019). The interaction of VLA-4 and the fibronectin CS1 peptide was demonstrated to be functionally important in the process of transendothelial migration of a leukocyte subpopulation *in vitro* (Kuijpers, T. et al. (1993) *J. Exp. Med.* 178:279), and has been used since then in numerous *in vivo* models.

The disclosure in the application showing delayed onset of diabetes supports claims to the treatment of diabetes

The Examiner alleges that the *in vivo* data provided in the specification is not drawn to treating mammals "with diabetes" and that "delayed onset of diabetes is not method of treatment of diabetes as defined by the specification." Appellant respectfully points out that the phrase "type I diabetes," as recited in claim 25, encompasses a prediabetic mammal or a mammal having partial β cell destruction. The terms "prediabetic," "overt diabetes," "diabetes onset," and "diabetic" as stages of type I diabetes are discussed in the specification as follows:

> The term "prediabetic" is intended to mean an individual at risk for the development of diabetes disease (e.g., genetically predisposed) at any stage in the disease process prior to overt diabetes or diabetes onset. The term "diabetic" is intended to mean an individual with overt hyperglycemia (i.e., fasting blood glucose levels $\geq$ 250 mg/dL). The term "overt diabetes" or "diabetes onset" is intended to mean a disease state in which the pancreatic islet cells are destroyed and which is manifested clinically by overt hyperglycemia (i.e., fasting blood glucose levels $\geq$ 250 mg/dL). (page 7, lines 19-25 of the specification)

Thus, the disclosed results apply to the treatment of diabetes in a stage of disease prior to overt hypergycemia, as well as mammals having partial cell destruction, e.g., mammals having ongoing disease. Appellant showed a delay in the onset of diabetes in prediabetic NOD mice, i.e., four weeks post-partum and prior to the onset of overt

symptoms. The application includes an adoptive transfer experiment where the administration of anti-VLA-4 antibody (R1-2) significantly inhibited onset of diabetes in a mammalian NOD mouse model with residual beneficial results extending as long as two months after cessation of administration of the anti-VLA-4 antibody (R1-2). (See, e.g. pages 16-18 of the specification). The specification also discloses on page 29, lines 26-30, that the adoptive transfer experiment described for the antibodies was repeated successfully with the soluble VCAM molecule, i.e., VCAM 2D-IgG. Moreover, Example 4 shows similar results to the ones shown in adoptive transfer experiments in a spontaneous diabetes mouse model administered rat anti-mouse VLA-4 antibodies twice weekly for 8 weeks. The onset of diabetes was significantly delayed (12-16 weeks delayed). The experiment in Example 4 was not an "adoptive transfer" experiment; rather, rat monoclonal antibody was directly administered to the subject NOD mice.

The results in Example 4 have been further corroborated by Yang et al. (1994) *PNAS* 91:12604-12608, in which the treatment of neonatal mice with anti-integrin alpha 4 monoclonal antibodies for the first 4 weeks of life led to a significant and long-term protection against spontaneous occurrence of insulitis and diabetes. Thus, the delay in the occurrence of diabetes initially demonstrated in "adoptive transfer" experiments has been corroborated in a spontaneous model for diabetes.

In a further aspect of the rejection, the Examiner cites Cohen et al. (Autoimmune Disease Models, A Guidebook, Academic Press, San Diego, 1994) (Paper 14, section 11, page 8), to support the proposition that the present specification does not enable a method of treating a mammal having partial β cell destruction. In particular, according to the Examiner, Cohen et al. teach that at 3-4 weeks of age, pancreatic islet β cells appear to be clear of infiltrating immune cells, which seem to localize to the blood vessels of the islets of NOD mouse pancreas. At 6-7 weeks, the infiltrating cells reach the islets surrounding them or accumulating at one pole and that between 10-12 weeks, the infiltrating cells penetrate the islets (p. 150 of Cohen et al.).

This aspect of the rejection is also traversed. Appellant showed that inhibition of the VLA-4-VCAM interaction prevented immune cell recruitment and thereby

destruction of pancreatic islet β cells. Thus, Appellant's results apply to the treatment of diabetes prior to overt diabetic symptoms, as well as mammals having partial cell destruction, e.g., mammals having ongoing disease.

Successful treatment of ongoing diabetes using VLA-4 inhibitors is confirmed by Yang *et al.* As shown in Yang *et al.*, treatment of NOD mice after the onset of insulitis from 10 to 14 weeks of age with an anti-integrin alpha 4 (VLA-4) antibody resulted in a significant and long-lasting suppression of an ongoing, late stage of the disease (*see e.g.*, Yang *et al. supra* at page 12607 and Fig. 5). In this regard, Yang et al. conclude:

> Furthermore, the fact that blockade of integrin α4 was effective in treating an ongoing diabetogenic process suggests that the progression of autoimmune inflammatory destruction of the β islet cells may require continuous recruitment of lymphocytes and/or inflammatory cells from the circulation. (emphasis added)

Thus, the present invention also enables methods of treating ongoing disease. NOD mice 10 to 14 weeks after the onset of insulitis show partial β cell destruction; therefore, methods of treating a mammal having partial β cell destruction using VLA-4 inhibitors are fully enabled.

The claimed methods are not "general immunosuppression"

In another aspect, In Paper No. 14, section 6, page 4, the Examiner states the following.

> it cannot be predicted how general immunosuppression would treat insulin dependent diabetes, [and] the specification does not teach methods of determining the appropriate dosages in order to selectively target pathogenic cells....

This ground of the Examiner's argument is also traversed. Immune cell migration is mediated by a myriad of interactions between cell surface molecules and counterligands. Such interactions include, for example, the combination of LFA-1 and VLA-4, and Mac-1 and VLA-4 on the surface of lymphocytes and macrophages, respectively, with the counterligands ICAM (for LFA-1 and MAC-1) and VCAM and

fibronectin (for VLA-4). Unlike non-specific immunosuppressive and/or immunomodulatory agents for treating diabetes, e.g., cyclosporin, known in the prior art (see background of the specification at pages 3-4), the present invention showed that by specifically blocking one interaction, the VLA-4-VCAM interaction, it is possible to prevent immune cell destruction of pancreatic islet β cells. Appellant's method, therefore, is not "general immunosuppression," but selective targeting.

Furthermore, a skilled artisan would know how to adjust the effective concentration of the fibronectin inhibitor to selectively target pathogenic immune cells. The VLA-4 receptor has been shown to have at least two distinct affinity states, a high and a lower affinity state, depending on the level of activation (see e.g., Jakubowski, A. et al. (1995) *Cell Adhesion and Communication* 3:131-142). When present on activated cells, e.g., pathogenic immune cells, VLA-4 shows higher affinity for its ligands compared to the affinity displayed by VLA-4 on resting cells. By adjusting the effective concentration of the fibronectin inhibitor, it is possible to selectively target those pathogenic cells.

It would be a routine matter for one of ordinary skill in the art to determine dosages and modes of administration of fibronectin.

The Federal Circuit has made it clear that, in considering whether a patent is enabling, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). In the present application, the determination of specific effective dose ranges and modes of administration of fibronectin would be a routine matter for one of ordinary skill in the art, in view of the guidance provided in the application with respect to dose ranges and modes of administration of VLA-4 inhibitors.

Specific effective dose ranges and modes of administration of VLA-4 inhibitors are provided in detail in the instant application (see e.g., page 13, lines 4-26). In addition, working examples describing the effectiveness of these inhibitor dosages are extensively

described (see e.g., Examples 1-5, pages 16-30). Fibronectin polypeptides were known inhibitors of VLA-4 activity at the time the present application was filed, as described above, and could have been effectively used to treat diabetes by following the teachings of the specification. The present application provides that dose ranges of non-antibody (e.g., peptide) inhibitors can be between molar equivalent amounts of the antibody dosages disclosed (see page 13, lines 12-13). These dosages can routinely be extrapolated to fibronectin. Furthermore, the instant application provides an example of how one would optimize or determine dosages by monitoring the coating of VLA-4 positive cells by the inhibitors over time after administration at a given dose *in vivo*. The determination of dosage is a routine matter for one of ordinary skill in the art. The Examiner has presented no evidence that the dosages suggested in the specification would be insufficient to enable the use of fibronectin peptides as claimed.

Treatment of diabetes in the NOD animal model, as described in the specification, is predictive of similar results in humans

On pages 9-12 of Paper 14, the Examiner relies on Atkinson *et al.* (1999) *Nature Medicine* 5:601-604 and Bowman et al. (1994) *Immunol. Today* 15:115-1120 to support the proposition that efficacy in the treatment of diabetes in the NOD animal model is not predictive of similar results in humans. This part of the rejection is respectfully traversed.

NOD mice are an art-recognized animal model for human type I diabetes. Bowman et al. list many key features of human type I diabetes that are reflected in NOD mice: (1) the development of insulitis; (2) the inheritance of particular major histocompatibility complex (MHC) class II alleles, representing the major component of genetic susceptibility; (3) the transmission of diabetes by hematopoietic cells in bone marrow; and (4) the T cell dependence of the disease pathogenesis.

The Bowman et al. reference further states (at page 19, last paragraph):

> The NOD mouse has provided a model system to study not only the pathogenesis and natural history of a disease that is similar to human IDD,

> but also a means with which to prevent the disease in humans. (emphasis added)

As outlined above, the NOD mouse model shares a number of important characteristics with human type I diabetes. The disease develops spontaneously and is not accompanied by general immunodeficiency as in some other animal models, e.g., the BB rat. Differences include simultaneous lymphocyte infiltration of salivary glands and other organs, and a strong female predominance. Despite these minor differences, the study of mechanisms involved in insulitis, β-cell destruction, and the generation of other immunological disturbances allows hypotheses concerning human type I diabetes to be developed and tested (see, e.g., Lampeter et al., *Diabetologia* 32:703-708, 1989).

Regarding the testing of new therapies, Pozzilli et al. (1993) *Immunology Today* 14(5): 193-196, states at page 196, last paragraph:

> All new therapies aimed at preventing Type 1 diabetes should first be tested on animal models of the disease and the NOD mouse is one of the most appropriate models for this purpose. (emphasis added)

Appellant demonstrated that molecules capable of blocking the interaction between VLA-4 and VCAM-1 delayed the onset of diabetes in a NOD mouse model. At the time the present application was filed, fibronectin polypeptides were known inhibitors of the VLA-4 activity. Once the Appellant established the correlation between inhibition of the VLA-4-VCAM interaction and the treatment of diabetes *in vivo*, one skilled in the art would have expected similar results using fibronectin polypeptides. Furthermore, there is no reason to believe that blocking the VLA-4-VCAM interaction in humans would not produce results similar to those observed in NOD mice.

The Tisch reference cited by the Examiner is not relevant to the pending claims

In Paper 14 at page 9, the Examiner cites Tisch *et al.* (1994) *PNAS* 91:437-438 to support the proposition that:

> In view of the known lack of success in treating insulin-dependent diabetes and the critical requirement of determining whether a treatment

can be used to treat an ongoing autoimmune response as taught it cannot be predicted, based on the information in the specification and the art, that the invention will function as claimed.

This aspect of the rejection is traversed.

Appellant clarifies that the statements about the lack of success in treating insulin-dependent diabetes refer to the Examiner's misinterpretation of the description in the background of the present application of the shortcomings of the prior art methods and compositions in treating diabetes. This statement does not refer to the present invention.

As to the Tisch reference, Appellant submits that this reference relates to the use of antigen-specific immunotherapy, i.e., induction of T cell tolerance by autoantigen immunization, in treating autoimmune disorders. This method is irrelevant to the present application. As described above, the present method is directed to the successful prevention of immune cell recruitment to pancreatic β cells using specific inhibitors of the VLA-4-VCAM interaction. The methods of the invention are completely different to the induction of T cell tolerance reviewed by Tisch et al.

For the reasons detailed above, Appellant submits that one of ordinary skill in the art could make and use the claimed invention using the specification as a guide. Therefore, Appellant respectfully submits that the claimed invention is enabled and requests that the Board reverse this rejection.

(B) The Scope Of Claims 25, 28, And 31-36 Would Be Clear To An Ordinary Skilled Artisan.

Claims 25, 28, and 31-36 stand finally rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. To support this rejection, the Examiner provides the following arguments: (1) claims 31 and 32 are indefinite in the recitation of "chimeric molecule" because the exact meaning of the word chimeric is not known; and (2) claims 25, 28, and 31-36 are indefinite because the preamble of claim 25

recites a method of treating insulin-dependent diabetes, whereas the method steps are drawn to a method of treating mammals that do not have diabetes.

Claims 31 and 32 are clear in the recitation of "chimeric molecule."

The claims are to "set out and circumscribe a particular area with a reasonable degree of precision and particularity." In re Moore, 439 F.2d 1232, 1235 (C.C.P.A. 1971). The definiteness of a claim must be analyzed "in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." Id. at 1235. Appellant submits that, in light of the prior art, the teachings in the present specification, and the level of skill in the art, claims 31 and 32 are not indefinite in the recitation of "chimeric molecule."

The Examiner states in Paper No. 10, section 10, pages 10-11:

> Claims 31 and 32 are indefinite in the recitation of "chimeric molecule" because the exact meaning of the word chimeric is not known. The term chimeric is generic to a class of molecules which are products of genetic shuffling of several other active proteins. The term encompasses soluble fibronectin polypeptides fused to other proteins as well as soluble fibronectin polypeptides wherein any domain of the polypeptide is substituted by corresponding regions from other VLA-4 blocking agents.

As pointed out by the Examiner, the term chimeric molecule is art-recognized to mean a class of molecules, which comprise different kinds of molecules linked to each other, e.g., fusions or substitutions. The fact that both fusions and substitutions are encompassed by this term does not render the term indefinite. The breadth of a claim is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 693 (CCPA 1971).

As described at pages 9-10 of the specification, a chimeric molecule, for purposes of the present invention, may include: (1) a VLA-4 targeting moiety; (2) optionally, a second peptide that increases solubility and *in vivo* life of the VLA-4 targeting moiety; and (3) a toxin moiety. Included as examples of VLA-4 targeting moieties are fibronectin, fibronectin having an alternatively spliced non-type III connecting segment, and fibronectin peptides containing the amino acid sequence EILDV or similar

conservatively substituted amino acid sequence. Members of the immunoglobulin superfamily or fragments or portions thereof are provided as examples of optional second peptides. The toxin moiety may be any agent that kills or inactivates a cell when it is targeted to the cell by the targeting moiety. Toxin moieties described in the present specification include: *Diphtheria* toxin A, *Pseudomonas* exotoxin, Ricin A, Abrin A, *Shigella* toxin, gelonin, radionucleotides, and chemotherapeutic agents.

Accordingly, the term "chimeric molecule would be clear to an ordinary artisan. Therefore, Appellant respectfully requests that the board reverse this rejection.

Claims 25, 28, and 31-36 are clear in the phrase "insulin dependent (type I) diabetes".

It is a well-established principle in patent law that a patentee is free to be his or her own lexicographer. See e.g., Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995); Hormone Research Foundation, Inc. v. Genentech, Inc., 904 F.2d 1558, 1563 (Fed. Cir. 1990); Autogiro Company of America v. United States, 384 F.2d 391, 397 (Ct. Cl. 1967). The phrase "insulin dependent (type I) diabetes" is clear in light of the definitions provided in the specification.

In the Final Office Action the Examiner states,

> in the absence of a specific definition of type I diabetes in the specification that includes prediabetic and mammals having partial beta cell destruction, it is assumed for examination purposes that the Type I diabetes claimed is the art recognized and specification defined Type I diabetes which is a disorder of carbohydrate metabolism, characterized by hyperglycemia and glyocuria and resulting from inadequate production or utilization of insulin." (section 6, pages 4-5).

Contrary to the Examiner's suggestion, it is clear from the plain language of claim 25 that the phrase "treatment of insulin dependent (type I) diabetes" refers to a broad range of stages of diabetes, including prediabetic mammals and mammals having partial β cell destruction, as specifically recited in claim 25.

Further, Appellant has defined several terms related to diabetes in order to accurately describe various aspects and degrees of this disorder. What the Examiner deems to be the definition of "type I diabetes" is defined in the specification as the "overt diabetes" stage of type I diabetes. See page 7, lines 23-25, where the terms "overt diabetes" and "diabetes onset" are defined to mean "a disease state in which the pancreatic islet cells are destroyed and which is manifested clinically by overt hyperglycemia (i.e., fasting blood glucose levels $\geq$ 250 mg/dL)." The term "prediabetic" is defined in the specification at page 7, lines 19-21 as "an individual at risk for the development of diabetes disease (e.g., genetically predisposed) at any stage in the disease process prior to overt diabetes or diabetes onset." Thus, it is clear from the teachings of the specification that the term "diabetes" refers to any stage of the disorder ranging from a prediabetic individual who may currently have only a genetic predisposition to an individual developing overt symptoms to an individual with "overt diabetes" manifested clinically by hyperglycemia. Therefore, as recited in claim 25, type I diabetes includes prediabetic mammals and mammals having partial beta cell destruction. When the specification states the meaning that the claimed terms are intended to have, the claims should be examined with that meaning to achieve a complete exploration of the invention and its relation to the prior art. In re Zletz, 893 F.2d 319, 321 (Fed. Cir. 1989). Given the teachings of the specification, it would be clear to a skilled artisan that the scope of the term "diabetes" in claim 25 includes prediabetic mammals and mammals having partial beta cell destruction.

For the reasons provided above, Appellant respectfully requests that the board reverse this rejection.

(9) Appendix of Claims

25. A method for the treatment of insulin dependent (type I) diabetes comprising administering to a prediabetic mammal, or a mammal having partial β cell destruction, a composition comprising a soluble fibronectin polypeptide, in an amount effective to treat diabetes.

28. The method according to claim 25, wherein the fibronectin polypeptide comprises an EILDV motif.

31. The method according to claim 25, wherein the fibronectin polypeptide is a component of a chimeric molecule.

32. The method according to claim 31, wherein the chimeric molecule further comprises a toxin moiety.

33. The method according to claim 25, wherein the mammal is prediabetic.

34. The method according to claim 33, wherein the prediabetic mammal is a human.

35. The method according to claim 25, wherein the mammal has partial β cell destruction.

36. The method according to claim 25, wherein the fibronectin polypeptide comprises an alternatively spliced non-type III connecting segment of fibronectin.

The required appeal fee of $320 under 37 C.F.R. §1.17(c) is enclosed. A Petition for Extension of time is also enclosed along with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 15, 2002

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(9) Appendix of Claims

25. A method for the treatment of insulin dependent (type I) diabetes comprising administering to a prediabetic mammal, or a mammal having partial β cell destruction, a composition comprising a soluble fibronectin polypeptide, in an amount effective to treat diabetes.

28. The method according to claim 25, wherein the fibronectin polypeptide comprises an EILDV motif.

31. The method according to claim 25, wherein the fibronectin polypeptide is a component of a chimeric molecule.

32. The method according to claim 31, wherein the chimeric molecule further comprises a toxin moiety.

33. The method according to claim 25, wherein the mammal is prediabetic.

34. The method according to claim 33, wherein the prediabetic mammal is a human.

35. The method according to claim 25, wherein the mammal has partial β cell destruction.

36. The method according to claim 25, wherein the fibronectin polypeptide comprises an alternatively spliced non-type III connecting segment of fibronectin.